REMARKS/ARGUMENTS

Claims 1, 3, 5-7, 11, 12 and 19 are pending in the above-captioned application. The following remarks are believed to be fully responsive to the Office Action.

THE REJECTIONS UNDER 35 U.S.C. § 103

SHOULD BE WITHDRAWN

Claims 1, 3, 5-7, 11, 12 and 19 rejected under 35 U.S.C. 103 (a) as being unpatentable over Unger, U.S. Patent No 6,033,645 ("Unger"). In response, Applicants submit that each of the rejections should be withdrawn for the reasons stated below.

The present invention claims a method of enhancing product homogeneity in the administration of a gas-containing contrast agent to a subject by continuous infusion. The contrast agent is administered by continuous infusion over an infusion period of 5-60 minutes, and is delivered from the upper extremity of an essentially vertically positioned syringe and is admixed with a flushing medium prior to administration to the subject.

The present invention has identified a solution to a problem associated with the administration of a gas-containing contrast agent to a subject by infusion. A problem with the continuous infusion of gas-containing diagnostic contrast agents over a long period arises from the tendency of gas-containing components to float, since this will lead to inhomogenities forming within vessels, such as power-driven syringes, which may be used to administer the contrast agent. This may, for example, lead to an increase in microbubble concentration in the upper part of such a vessel and/or to changes in size distribution occurring at various points within the vessel as larger microbubbles float more rapidly than smaller microbubbles. This problem increases with increased time of administration of the contrast agent. The Applicant has surprisingly found that by combining delivering from the top of a vertically positioned syringe and admixing with a flush medium prior to administration to a patient, the segregation is minimized and enhanced product homogeneity

is achieved. By using a syringe as the delivery reservoir and placing this in a vertical position, with the outlet pointing upwards, the effects of floatation separation is greatly reduced, as further explained in the specification on page 3 and 4. The admixing with a flushing medium further enhances the homogeneity of the contrast agent that is delivered to the patient, e.g. by reducing the residence time of the agent in connecting tubes etc. It is further preferred that the syringe is positioned so that the bulk flow direction of the gas-containing contrast agent during expulsion is the same as the direction of segregation of the dispersed gas-bubble phase, i.e. upwards, since this will assist in counteracting the formation of concentration gradients of the dispersed gas-bubbles during administration. The claimed invention hence provides a method of administration wherein enhanced product homogeneity is achieved by combining the features of delivery of the contrast agent from the upper extremity of a vertically positioned syringe, and admixing this with a flushing medium prior to administration to the patient.

Unger discloses ultrasound contrast agents and delivery of such to a patient. The problem of Unger is to administer a contrast agent to a patient and generate an image without artifacts. As a solution Unger describes that diagnostic artifacts such as shadowing may be reduced by controlling the rate of administration of the contrast agent and/or by administering a flush such as normal saline after administration of the contrast agent. The contrast agent of Unger is typically administered over a period of 5 seconds (column 45, line 20), or up to a period of 50 seconds ((column 3, line 55), and any subsequent flush is typically administered over a period in the range 10 seconds to 10 minutes. To promote the transport of the contrast agent from the injection site into the bloodstream, a flush may be administered to push or wash the contrast agent into the bloodstream (page 70).

Unger discloses a different problem than the problem of the current invention. The problem of Unger is to avoid artifacts in an image. His solution to this problem is to control the rate of administration of the contrast agent. The motive for controlling the administration rate and period is hence different from the motive of the present invention. The method of Unger does not suggest infusion in a period of up to 1 hour and does not motivate for

administration over such long period. To avoid artifacts in the image Unger clearly suggests to administer the contrast agent over a period of seconds.

Further, the method of Unger for avoiding artifacts in an image would not work for infusion in up to 1 hour for enhancing product homogeneity. There is no teaching by Unger that the syringe should be positioned vertically for upright delivery of the ultrasound contrast agent, combined with that the contrast agent should be admixed with a flushing agent prior to administration. Figure 1 and Figure 2 of Unger position a syringe either for downward or upward delivery of a contrast agent. There is however no teaching about whether or why a syringe should be positioned in either direction, i.e. there is no indication by Unger that the administration direction of the contrast agent should be linked to the segregation direction of the contrast agent components. As the problem of Unger is different from the problem of the present invention, and as there is no teaching of why the syringes in Figures 1 and 2 are positioned as they are, the position of the syringe in the solution to the problem of Unger appear irrelevant. As disclosed for the administration related to Figure 2, the flush agent is administered after ejection of the contrast agent, and serves to push or drive the contrast agent into the patient (column 51, lines 35-56). There is no indication that the set up of Figure 2 could be used in a method of enhancing product homogeneity by admixing a contrast agent from the upper extremity of a vertically positioned syringe with a flushing agent.

The Examiner's argues that it would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the rate of administration of the contrast agent of Unger, and to have a reasonable expectation of success in achieving optimal images by determining the optimal rate of infusion. The Applicant respectfully submits that the skilled in the art reading Unger, could optimize the rates of administration and achieve optimal images without artifacts. However, Unger does not provide any motivation for the skilled man to modify the teaching of this reference to a method of achieving enhanced product homogeneity in infusion administration of a contrast agent over a period as long as up to 1 hour. The "optimizing" in the two documents refer to different aspects; Unger wants to

optimize rates/doses to provide images without artifacts, while the present invention wants to optimize homogeneity in the administration to provide a steady state of gas-containing contrast agent to enable imaging over a long time. Further, there is no reasonable expectation of success in achieving enhanced product homogeneity in infusion administration of a contrast agent over a period as long as up to 1 hour by modifying Unger. The Applicant respectfully submits that the Examiner's argument that Unger properly addresses all the limitations of the instant claims, except the infusion period of 5-60 minutes which may be optimized, can only be made with the benefit of application of hindsight.

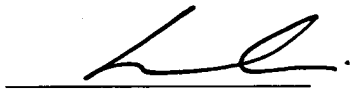
It is therefore respectfully submitted that 35 U.S.C. 103 rejections of claims 1, 3, 5-7, 11, 12 and 19 over Unger be withdrawn.

CONCLUSION

In view of the amendments and remarks herein, applicants believe that each ground for rejection or objection made in the instant application has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the current application are respectfully requested.

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,



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